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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/697,535	10/30/2003	David T. Curiel	678503-2001.1	7880

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EXAMINER	
PRIEBE, SCOTT DAVID	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 07/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/697,535	CURIEL ET AL.	
	Examiner	Art Unit	
	Scott D. Priebe, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 May 2004 & 10 Jan. 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 May 2004 & 10 Jan. 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20041007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The instant application is a continuation-in-part of 09/569,789. The instant application adds subject matter directed to the conditional regulation of the claimed conditionally-replicative adenovirus (CRAd) described in the '789 application wherein an adenoviral early gene is placed under control of a VEGF, survivin, or CXCR4 promoter. These new embodiments are recited specifically in claims 9 and 23. Claims 1-8, 10-22, and 24 are generic to these embodiments. Although the generic terminology used in the instant claims is the same as used in the '789 application, the meaning of the generic terminology has changed due to the inclusion of the previously undisclosed embodiments. These new embodiments were also not described in 60/133,634. The '634 application does not describe any fiber modifications other than insertions into the HI loop. Consequently, claims 1-24 are not directed to the same invention as described

in the '789 application and do not have benefit of priority to the '789 application, and the effective filing date of the instant claims is 10/30/03.

Specification

The disclosure is objected to because of the following informalities: Page 19, line 6, recites an amino acid sequence that has not been identified by its assigned SEQ ID NO as per 37 CFR 1.821(d).

Appropriate correction is required.

Claim Objections

Claims 7 and 21 are objected to because of the following informalities. The claims recite an amino acid sequence that has not been identified in the claims by its assigned SEQ ID NO as per 37 CFR 1.821(d). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining enablement are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation....Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (Wands, 8 USPQ2d 1404). Factors that can be used in evaluating undue experimentation include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

The claimed invention is broadly drawn to methods and compositions comprising an infectivity-enhanced conditionally-replicative adenovirus (CRAd) with enhanced infectivity toward a specific cell type as a consequence of introducing a ligand into the HI loop of the fiber of a wild-type adenovirus or replacing the fiber with a substitute protein presenting a targeting ligand and further comprising a conditionally regulated early gene designed to limit replication either to a specifically redirected tropism conferred by the modified fiber or substitute protein and/or by the cell type-specific expression of a conditionally regulated early gene or mutant thereof to limit adenoviral replication to that specific cell type. Further, the claims broadly embrace CRAds exhibiting infectivity-enhanced conditional replication in both *normal cells and tumor cells* and are further drawn to adenoviruses containing a modified fiber or a non-fiber

"substitute protein" presenting a targeting ligand to limit replication to a specific cell type targeted by the redirected tropism.

The specification teaches modifying the fiber by inserting a ligand, such as an RGD-containing peptide, physiological ligand, anti-receptor antibody, or cell-specific peptide, into the HI loop of the fiber (serotype C adenovirus, e.g. Ad5); replacing the knob portion of the fiber with that of an adenovirus of a different serotype that does not require the CAR receptor for infection, e.g. of Ad3; or replacing the fiber with a non-fiber protein that forms a trimer, such as phage T4 fibritin, isoleucine trimerization motif or neck region peptide of human lung surfactant D, with a targeting ligand attached to the C-terminus of the fiber protein. It teaches modifications that confer conditional regulation of replication of the adenovirus by mutational inactivation or deletion of the E1B 55k protein gene or mutation of E1A to inactivate the Rb binding site in E1A, or placing the E1A region under control of a "tumor-specific" promoter, such as the promoter listed in claim 9.

The specification fails to provide sufficient guidance teaching how to make or use a single adenoviral embodiment whose replication is limited to a "specific" cell type as recited in claim 1. There are no working examples describing an adenovirus exhibiting both redirected tropism and conditional early gene-mediated cell type-specific replication in the cell to which the redirected tropism is directed that would limit replication of the CRAd to a specific cell type. In their review of viral vector targeting, Peng and Russell teach:

> "[i]t is important to remember that retargeted vectors may have more than one binding specificity, being capable of binding not only to the targeted molecule but also to the natural receptor that is recognized by the unmodified vector coat protein. Thus, there will be no substitute for empirical in vivo studies to determine how these binding modifications will influence vector localization" (Curr. Opin. Biotech., 10:454-457, 1999; p. 454, right col.).

Although the specification teaches the *principle* of coxsackie-adenovirus receptor (CAR)-independent gene transfer by inserting a ligand in the HI-loop of the fiber (e.g. RGD insertion, Example 8) to redirect tropism in a CAR-independent manner, it admits that "the RGD-modification described here does not preclude the binding of the fiber to CAR, and the modified virus can enter the cells through α_v integrins and CAR" (p. 74, lines 2-4). In order to meet the limitations of claim 1 drawn to an adenovirus whose replication is limited to a specific cell type, the specification would have to provide sufficient guidance for making and using an adenovirus with a CAR-ablated phenotype, a new *cell type-specific* tropism, and/or a selective ability to replicate in one specific cell type to the exclusion of all others. Insertion of the RGD peptide into the HI loop does not reduce the host cell range of the CRAd as compared to a wild-type Ad5 fiber, it expands the host cell range. Similarly, replacement of the knob of an Ad5 fiber with that of Ad3 would expand the host cell range of the CRAd.

Although the specification teaches that "the adenovirus fiber amino acids crucial for CAR-binding abrogation and new tumor-selective peptides have been defined" (lines 7-9) the specification does not teach how to design such CAR-ablated, tumor cell redirected viruses, nor does the evidence of record provide any indication of any tumor-selective peptides capable of cell-type specific targeting. Pasqualini et al. (Nature Biotech., 15:542-546, 6/97) describes tumor-homing peptides that target $\alpha v\beta 3$ integrins expressed on the apical surface of endothelial cells in blood vasculatures surrounding various different tumors. In fact, Pasqualini teaches that the peptide (CDCRGDCFC; SEQ ID NO:1) utilized in the Example 8 of the instant specification and recited in claims 7 and 21, preferentially targets blood vessels of certain tumors (e.g. subcutaneous murine B1615b melanoma). However, the specification does not teach e.g. how to

make adenoviruses exhibiting conditional replication using endothelial cell-specific promoters. Moreover, at the time of filing, it was known that peptides identified by phage display for use as tumor homing agents exhibit unique patterns of selective organ targeting despite being similarly directed to endothelial cells (Rajotte et al., J. Clin. Invest., 102(2):430-437, 7/98). However, the specification provides no evidence that the peptide of SEQ ID NO: 1 is capable of cell-type specific targeting and infectivity (no biodistribution studies presented) or nor does the specification provide evidence that αvβ3 integrins are *only present in endothelial cells* so as to limit replication to endothelial cells. Thus, even if the specification had taught how to make adenoviruses with CAR-independent binding, it fails to provide sufficient guidance demonstrating that such viruses could be made to exhibit cell-type specific replication.

The specification does provide a working example of an adenovirus comprising an anti-fiber antibody conjugated to fibroblast growth factor-2 (FGF2) for redirecting tropism to cell containing FGF2 receptors (Example 1). However, the instant claims are not drawn to adenoviruses comprising conjugates such as these since the wild-type fiber is still present. However, even if they were, there is no evidence of any one specific cell type carrying an FGF2 receptor to the exclusion of all other cell types. The specification does not provide any *specific* examples of a ligand (e.g. peptide) for use in the claimed invention that would confer selective infectability--and by extension, cell-type specific replication on such cells.

The specification further fails to provide a sufficiently enabling disclosure commensurate with the scope of the claimed subject matter as it relates modifying the tropism of adenoviruses by inserting ligands into the HI loop of the fiber or replacing the fiber with a "substitute protein" presenting a targeting ligand that would also retain a trimeric structure, binding to the penton

base, and still be capable of promoting the assembly of functional, targetable capsid. The specification provides virtually no guidance concerning the specific nature of any ligands for use in the claimed methods or compositions selected from the group consisting of physiological ligands, anti-receptor antibodies, or cell-specific peptides, nor does it provide guidance concerning structural constraints which limit the extent to which ligands can be introduced into the HI loop so as to maintain a structurally appropriate functional fiber trimer capable of mediating capsid assembly into functional and mature viral particles. For example, at the time the invention was made, Dmitriev et al. (J. Virol., 72(12):9706-9713, Dec. 1998) reported that "[w]hereas we have demonstrated the utility of small peptides to be incorporated into the HI loop of the fiber knob, the size restrictions of this locale have not been fully defined" (p. 9712, right col.). Moreover, with regard to insertions in the HI loop, co-inventor Curiel was quoted at the time of filing as stating that:

> "[t]he size constraints of ligand incorporation at this site are yet to be determined; therefore, incorporation of large ligands such as EGF and sFvs is currently being investigated. However, it is likely that the sheer size of the sFv will require an alternate strategy such as complete replacement of the entire knob region.
>
> Ultimately, for true targeting to be achieved, modification to ablate native tropism will need to be addressed. It may be that incorporation of large ligands into the HI loop will simultaneously ablate native tropism by steric hindrance; however if this is not the case, further modifications will be required....if complete replacement of the knob with a targeting and trimerization moiety could be achieved, it would simultaneously ablate native tropism" (Curiel, Ann. NY Acad. Sci., 886:pp. 167-168, 1999)

Thus, the evidence from the prior art as taught by Curiel and Dmitriev, reveal that the full scope of the claimed embodiments were not enabled at the time the invention was made; therefore, the full scope can only be considered an invitation to experimentation, wherein the specification provides insufficient guidance or predictability for making and using the claimed embodiments.

With regard to the untested proposal to design adenoviruses containing artificial non-fiber substitute proteins for redirected cell tropism, the specification claims that "a person having ordinary skill in this art would be able to construct an artificial [fiber substitute] protein" (p. 19, lines 7-24). However, the specification fails to provide specific guidance on how to make or design redirected adenoviruses carrying such artificial proteins, nor does it provide a predictable basis for making such functional adenovirus embodiments in the absence of undue experimentation given that this has not been done before and given the uncertainty concerning structural constraints and/or size restrictions associated with maintenance of an appropriate trimerized structure capable assembling into a functional viral particle that can enter and translocate to the nucleus. Given that no such adenoviruses were described in the art at the time of filing, success in achieving such a proposal is highly unpredictable.

Laquerre et al. (J. Virol., 72:9683-9697, Dec. 1998) had previously attempted to design a retargeted HSV vector using a strategy analogous to that disclosed in the instant specification. Briefly, Laquerre attempted to make three different types of recombinant HSV-1 virions wherein the heparin sulfate binding domain (HSBD) of gC, responsible for mediating cell attachment, was replaced with the erythropoietin binding domain to redirect the modified HSV virion to EPO receptor bearing cells. Laquerre first attempted to specifically insert an exogenous targeting domain comprising an internally placed EPO coding region, inserted in place of the HSV gC HSBD. However, Laquerre was not able to observe any EPO-mediated binding using a chimeric gC:EPO with an internally positioned EPO sequence. However, upon replacement of the N-terminal 162 amino acids of gC comprising the HSBD with EPO Laquerre was able to produce a chimeric EPO-gC fusion protein that could be incorporated into HSV particles and used to direct

attachment of recombinant HSV virions resulting in non-productive infection. By electron microscopy, Laquerre was able to observe evidence of viral entry into pre-lysosomal vesicles, where particle degradation appeared to occur. The results of this study are consistent with the notion that modification or substitution of an adenoviral fiber with a non-natural ligand or artificial substitute protein presenting a targeting ligand is highly unpredictable with respect to infectability and/or expression of transgenes carried by the virions. It is important to emphasize that Laquerre was only able to observe chimeric HSV virions attaching, but not infecting EPO receptor bearing target cells, *and only when replacing the entire N-terminal 162 amino acids of gC*; when Laquerre attempted to replace *just the HSBD* (i.e. aa 83-161), *no EPO receptor-mediated binding was found to occur*. The specification does not sufficiently teach which targeting domains can be incorporated into the claimed compositions so as to preserve the targeting, infectability, nuclear translocation, and replication of cells. To enable the broad range of embodiments embraced by the claimed subject matter would require undue trial and error experimentation without the benefit of guidance from the specification. The specification does not provide any *a priori* basis for determining which targeting ligands or substitute proteins would facilitate proper assembly of functional adenovirus particles for use in the claimed methods.

Even if a properly assembled adenoviral particle could be made, there is no reason to suggest that targeting an adenovirus to a non-native receptor would allow the appropriate trafficking of the adenoviral particle to the nucleus to allow replication and/or transgene expression to take place. Many receptor-mediated pathways are degradative, leading to destruction of ligands (or viral particles) in lysosomes, as seen in the case when using the EPO-

receptor-directed HSV virions of Laquerre. Further, there is no evidence to suggest that an adenoviral particle re-routed through a non-native receptor-mediated pathway would be able to similarly exert its endosomolytic properties and trafficking to the nucleus as in the case following attachment and uptake following attachment to integrins and entry through the coxsackie-adenovirus receptor. The specification does not provide any experimental basis for infection and replication of adenoviral particles re-routed through non-native uptake pathways in a non-CAR mediated fashion.

The specification further fails to provide a sufficiently enabling disclosure teaching how to make CRAds whose replication is limited to a specific cell type based upon a "conditionally-regulated early gene." As indicated above, the specification teaches general modifications that alter the replication efficiency with respect to cell type. The first are loss of function mutations in the coding sequence of E1A or E1B proteins. These are attenuating mutations that reduce the efficiency of replication of the an adenovirus in a normal cell to a greater extent than they reduce replication efficiency in a tumor cell. These mutations would not limit replication of the CRAd to a specific cell type. The claims broadly embrace mutations in coding regions of other early genes, such as E2, E3 and E4 genes that would result in conditional regulation of replication. However, the specification fails to disclose any such mutations nor does the prior art, other than loss of essential E2 or E4 function requiring replication in a "specific cell type" such as a complementing cell line that provides the missing E2 or E4 gene product in *trans*.

Second, the specification teaches conditionally replicative on account of operably linking a heterologous tissue-specific promoter to adenoviral early genes. Although prophetic Examples 10 and 11 provide guidance teaching the use of a prostate specific antigen, neither these

examples, nor any of the other teachings in the specification provide a sufficiently enabling disclosure for limiting replication in accordance with the breadth of the claims or the choice of a given tissue (or tumor)-specific promoter. First, the specification provides little guidance concerning which promoters to use in the methods of the claimed invention. Secondly, the specification fails to provide evidence of having overcome one of the problems of using tissue-specific promoters *in vivo*. Babiss et al. (J. Mol. Biol., 193:643-650, 1987) have previously shown that liver cell-specific promoters inserted in a *replicative adenovirus* exhibit reduced specificity compared to their normal activities in a cellular context; although cell-specific expression from certain promoters was not significantly changed in certain cell types when placed in a replicating adenoviral background, delivery to other non-liver cells (i.e. HeLa) resulted in high levels of transgene expression, independent of the "tissue-specific" promoter chosen (see e.g. abstract). These results are consistent with the more recent findings of Shi et al. which suggest that negative elements are present in the adenoviral genome that appear to negatively impact on the specificity of heterologous tissue-specific promoters inserted into adenoviral vectors (Shi et al., Hum. Gene Ther., 8:403-410, March 1997). Also see, Molnar-Kimber (WO 01/23004) at page 5 for example. In the absence of further guidance and/or working examples related to choice of cells and promoters that do *not* reduce promoter specificity when inserted in an adenoviral vector such that replication specificity is also not lost, the practice of using the claimed embodiments in accordance with the recited limitations (i.e. tissue or (tumor)-specific replication) is highly unpredictable. Failure to maintain specificity of expression would likely ensure that replication is not limited to the particular cells targeted by the operably linked tissue (or tumor)-specific promoter as required by the recited limitations in

the instant claims. While CRAds whose replication is regulated by "tumor-specific" promoters have been shown to replicate more efficiently in tumor cells than in most normal host cells, there is no evidence of record that replication of such CRAds is limited to tumors cells.

Except for claim 2 and possibly claim 16 (see rejection under 112, second para.), the claims embrace CRAds whose replication is limited in any specific cell type whether normal or not, which would include neurons, muscle cells, macrophages, liver cells, etc. The specification teaches only using the CRAds for killing of tumor cells, such as for treatment of cancer. The specification does not suggest or teach how to make a CRAd whose replication is limited to any specific cell type other than tumor cells, nor does it suggest or teach any method of "adenoviral gene therapy" for treating any other disease than cancer. At best, the specification teaches how to make CRAds that replicate more efficiently in tumor cells than in most normal cell types, and how to use such CRAds in treatment of cancer.

The specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman*, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991). For the reasons above, the instant specification fails to do so. The guidance and working examples provided in the specification are not commensurate in scope with the breadth of the invention being claimed with respect to the modification or replacement of the fiber protein in order to enhance infectivity, the modification of early genes in order to limit the replication of the CRAd, and the object of the gene therapy. In view of these considerations, the lack of teachings in the specification and prior art on how to "limit" replication of an adenovirus to a specific cell type, and the unpredictability in this art, undue experimentation would be required.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 16 recites the limitation "said cell". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the

reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-5, 8, 9, 13, 15-19, 22, and 23 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Takayama et al. Mol. Ther. 7(5, Part 2): S420, abstract 1089, as evidenced by Curiel et al., WO 00/67576.

Takayama discloses treatment of lung cancer with a CRAd comprising an E1 region under control of the human VEGF promoter and modification of its fiber by replacement of the knob with that of Ad3. Curiel is illustrative of the state of the CRAd art at the time Takayama was published, and shows that at this time one of skill in this art was aware of how to prepare CRAds and administer them in treatment of cancer.

Claims 1-5, 8-10, 13, 15-19, and 22-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Curiel, D.T. (Proc. Amer. Assoc. Cancer Res. Ann. Meet. 43: 662-663, abstract 3287, March 2002), as evidenced by Curiel et al., WO 00/67576.

Curiel (2002) generally describes CRAd for use in treatment of cancer comprising a fiber modified by insertion of ligands into the HI loop or by replacement with the knob of an adenovirus of another serotype, wherein the E1 region of the CRAd is placed under control of a tumor specific promoter, such as the VEGF promoter, and the CRAd may contain a heterologous therapeutic gene, encoding a heat shock protein that increases increase potency of the CRAd. WO 00/67576 is illustrative of the state of the CRAd art at the time Curiel was published, and shows that at this time one of skill in this art was aware of how to prepare CRAds and administer them in treatment of cancer. Although Curiel (2002) does not explicitly disclose how the CRAd

is administered, the administration routes listed claim 14 cover nearly all methods of administering CRAd.

Claims 1-8, 10-22, and 24 are rejected under 35 U.S.C. 102(b) & (e) as being anticipated by Wickham et al. (U.S. 5,846,782, issued 12/8/99), as evidenced by Imler et al. (Gene Ther. 3: 75-84, 1996) with respect to claim 2.

Wickham et al. disclose an infectivity-enhanced conditionally replicative adenovirus possessing enhanced infectivity towards a specific cell type relative to wild-type adenovirus due to introduction of a peptide having the sequence CDCRGDCFC into the HI loop of the fiber of said wild-type adenovirus wherein said infectivity-enhanced conditionally-replicative adenovirus has at least three conditionally regulated early genes such that replication of said adenovirus is limited to said the specific cells infected by said adenovirus (see e.g. claims 12, 14, 16, and 17 in relation to SEQ ID NO:3). Wickham teaches that in view of the crystal structure of the fiber knob, the protein fiber loop regions of the HI loop offer a particularly desirable region for insertion of specific peptides, including those having the sequence CDCRGDCFC (i.e. SEQ ID NO:3; see col. 7, line 49 through column 8, line 66), previously described in the literature as binding with about 100-fold higher affinity to αv integrins compared to similar linear RGD motifs (col. 30, lines 20-22). Wickham teaches that the adenoviral vectors employed for gene transfer can be replication defective for normal cells due to inactivation of the E1 region are conditionally replicative in a specific cell type - one that provides E1 gene products in *trans* such as 293 cells (Example 7, starting at col. 30). Additionally, Wickham teaches that the adenoviral vectors of the claimed invention can carry a therapeutic gene exerting its therapeutic effect

through expression of a HSV thymidine kinase gene rendering cells selectively sensitive to the killing action of gancyclovir (col. 14, lines 50-57), and using such vectors to treat cancer (col. 17, lines 2-35).

Adenovirus that are replication-defective in normal cells, such as the E1-deleted adenoviral vectors of Wickham, have E2 and E4 genes, for example, that are conditionally regulated in cells that carry E1 complementing sequences, e.g. 293 cells or the E1-complementing A549 (a tumor cell) of Imler. Replication of these E1-deleted adenovirus is restricted to cells of the specific type that express products that complement deletion of E1. Thus, these types of vectors meet the limitation for a conditionally regulated early gene as it is defined in the specification (pages 21-22, bridging para.). Limiting the claims to unequivocally exclude what are generally called replication-defective adenovirus would overcome this rejection. For example, the independent claims could be limited to conditional regulation due to the disclosed specific mutations of E1A or E1B coding regions or a functional E1A region under control of a tumor specific promoter. The term "tumor specific" is used loosely here only to mean a promoter that over-expresses in a tumor cell relative to the normal cell type from which it arose.

Claims 1-4 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Stevenson et al. (J. Virol., 71(6):4782-4790, June 1997)), as evidenced by Imler et al. (Gene Ther. 3: 75-84, 1996) with respect to claim 2.

Stevenson discloses an infectivity-enhanced conditionally replicative adenovirus possessing enhanced infectivity towards specific clinically relevant target tissues as compared to

wild-type Ad5 due to replacement of the Ad5 fiber head domain comprising an HI loop with a homologous Ad3 fiber head domain wherein said infectivity-enhanced conditionally-replicative adenovirus has conditionally regulated E2 and E4 gene carrying their endogenous promoters directing conditional expression and replication of said adenovirus to specific cells infected by said adenovirus and carrying the appropriate cellular and/or transacting factors for E2 and E4 expression and by extension, viral replication (see e.g. abstract and "Materials and Methods, p. 4783, left col.), namely specific cell types that provide E1 gene products in *trans* such as 293 cells or the E1-complementing A549 (a tumor cell) of Imler. See the rejection over Wickham above for suggestions to overcome this rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4, 6, 7, 10-14, 18, 20, 21 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takayama et al. (Mol. Ther. 7(5, Part 2): S420, abstract 1089) in view of Curiel et al., WO 00/67576.

Takayama has been described above. In addition, Takayama teaches an embodiment wherein a HSV tk gene is co-administered with the CRAd in a "non-replicative" adenoviral vector, which produces a synergistic anti-cancer effect. Takayama does not teach to modify the fiber by insertion of an RGD-containing peptide into the HI loop, to include the HSV tk gene in the CRAd or any particular route of administration of the CRAd, although it is noted that the various routes of administration recited in claim 14 cover nearly all routes commonly used in treating cancer by gene therapy in general and CRAds in particular.

However, Curiel teaches that as an alternative to replacing the knob portion of the fiber with that of a different adenovirus, one can overcome the reduced infectivity of tumor cells by adenovirus due to loss of CAR in the tumor cell by genetically altering the fiber gene of the CRAd so that a CDCRGDCFC oligopeptide is inserted into the HI loop (e.g. pages 21-22). Curiel also teaches to include a therapeutic gene, such a gene encoding HSV tk, in the CRAd to provide an additional means of killing tumor cells in a patient. Gancyclovir is administered following administration of the CRAd. To effect treatment of cancerous tumors, CRAds are administered intravenously , intraperitoneally, systemically, orally or intratumorally. See for example, pages 23-24.

Therefore, it would have been obvious at the time the invention was made to have modified the fiber of the CRAd of Takayama by insertion of an RGD peptide into the HI loop,

rather than be replacement of the fiber knob, since Curiel taught that this modification was a suitable alternative for improving infectivity of a tumor cell by a CRAd and one knew how to make such a modification. It also would have been obvious to have included the HSV tk gene in the CRAd, rather than on a separate vector, since Curiel taught that such a modification of a CRAd was useful for treating cancer, and including the tk gene in the CRAd would eliminate the necessity of preparing two separate adenovirus and improve the frequency of co-transfection of a tumor cell by both CRAd and HSV tk gene to provide an additional means to kill tumor cells. Finally, it would have been obvious to have administered the CRAd by the various routes recited in instant claim 14 because Curiel taught that these routes were suitable for treating cancer.

Claims 1, 4, 6, 7, 10-14, 18, 20, 21 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curiel, D.T. (Proc. Amer. Assoc. Cancer Res. Ann. Meet. 43: 662-663, abstract 3287, March 2002) in view of Curiel et al., WO 00/67576.

Curiel (2002) has been described above. Curiel does not teach to modify the fiber by insertion of an RGD-containing peptide, specifically, into the HI loop, to include the HSV tk gene in the CRAd or any particular route of administration of the CRAd, although it is noted that the various routes of administration recited in claim 14 cover nearly all routes commonly used in treating cancer by gene therapy in general and CRAds in particular.

However, WO 00/67576 teaches that one can overcome the reduced infectivity of tumor cells by adenovirus due to loss of CAR in the tumor cell by genetically altering the fiber gene of the CRAd so that a CDCRGDCFC oligopeptide is inserted into the HI loop (e.g. pages 21-22). WO 00/67576 also teaches to include a therapeutic gene, such a gene encoding HSV tk, in the

CRAd to provide an additional means of killing tumor cells in a patient. Gancyclovir is administered following administration of the CRAd. To effect treatment of cancerous tumors, CRAds are administered intravenously, intraperitoneally, systemically, orally or intratumorally. See for example, pages 23-24.

Therefore, it would have been obvious at the time the invention was made to have modified the fiber of the CRAd of Curiel by insertion of an RGD peptide into the HI loop, since WO 00/67576 taught that this modification was effective for improving infectivity of a tumor cell by a CRAd and one knew how to make such a modification. It also would have been obvious to have included the HSV tk gene in the CRAd, since WO 00/67576 taught that such a modification of a CRAd was useful for treating cancer to provide an additional means to kill tumor cells. Finally, it would have been obvious to have administered the CRAd by the various routes recited in instant claim 14 because WO 00/67576 taught that these routes were suitable for treating cancer.

Claims 1-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Molnar-Kimber, WO 01/23004 in view of Curiel et al., WO 00/67576.

Molnar-Kimber teaches CRAds and methods of using the CRAds for the treatment of cancer (e.g. pages 8-12, claims 1-32). The CRAds comprise an E1A gene under control of a tumor specific promoter, such as the survivin promoter (e.g. page 11, ¶ 1; claims 5 and 18) to render the CRAd conditionally-replicative in tumor cells. The CRAd may also contain a therapeutic gene encoding HSV tk to augment the oncolytic activity, where gancyclovir is also administered (e.g. page 16, lines 7-12; page 30, lines 3-16). For treating cancer, the CRAd is

administered intravenously, intraperitoneally, systemically, orally or intratumorally (page 31, lines 13-24). Molnar-Kimber does not teach to modify the adenoviral fiber either by insertion of an RGD peptide into the HI loop or by replacing the knob with that of a different adenovirus.

However, Curiel teaches that the loss of CAR in tumor cells reduces the infectivity by adenovirus, thereby reducing the effectiveness of treating cancer with CRAds having a wild-type fiber (page 19). Curiel teaches that this reduced infectivity of tumor cells by adenovirus due to loss of CAR in the tumor cell can be overcome by genetically altering the fiber gene of the CRAd so that a CDCRGDCFC oligopeptide is inserted into the HI loop (e.g. pages 21-22) or the knob is replaced by that of an adenovirus that binds to receptors other than CAR, e.g. of Ad3.

Therefore, it would have been obvious at the time the invention was made to have modified the fiber of the CRAd of Molnar-Kimber by insertion of an RGD peptide into the HI loop or by replacement of the fiber knob with that of a different adenovirus, since Curiel taught that loss of CAR by tumor cells reduced the infectivity of CRAds (based on Ad 5) and that these modifications of the fiber were effective for improving infectivity of a tumor cell by a CRAd, and one knew how to make such a modification.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-8, 10-22 and 24 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 6,824,771. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims embrace the subject matter claimed in the '771 patent.

Claims 1-8, 10-22, and 24 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 9, 11, 16, 22, 23, and 26-29 of copending Application No. 09/245,603, as evidenced by Imler et al. (Gene Ther. 3: 75-84, 1996). PTO records indicate that the instant application, when filed, was commonly assigned with the '603 application.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '603 application embrace explicitly claimed embodiments of the instant application (both adenovirus and methods of treatment) wherein the adenovirus is infectivity enhanced due to genetic modification of the fiber gene resulting in insertion of an RGD peptide into the HI loop of the fiber protein. While the claims of the '603 application are not explicitly limited to adenovirus having a conditionally regulated early gene that limits replication of the adenovirus to specific cell types, as are the instant claims, this limitation, as it is defined in the instant specification (pages 21-22, bridging para.), does not substantially differentiate the instantly claimed subject matter from that of the '603 application. An adenovirus

that is wild-type has conditionally regulated early genes normally, which restricts its replication to specific cell types, e.g. to human cells in the case of hAd5 and not cells of most other mammals, birds or reptiles. Also, adenovirus that are replication-defective in normal cells, such as the E1-deleted Ad5 vectors exemplified in the '603 application, have E2 and E4 genes, for example, that are conditionally regulated in cells that carry E1 complementing sequences, e.g. 293 cells or the E1-complementing A549 (a tumor cell) of Imler. Replication of these E1-deleted adenovirus is restricted to cells of the specific type that express products that complement deletion of E1. The '603 application discloses use of the specific RGD peptide of instant claims 7 and 21, and so when its claims are read in light of their supporting disclosure this embodiment is clearly included.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe, Ph.D. whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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